## REMARKS

Claims 1-40 are currently pending. Claims 6, 10-13, 21, 25-28, 33 and 37-40 are withdrawn without prejudice to their rejoinder in this application or prosecution in another application. Claims 1, 14 and 29 are amended to more clearly describe the claimed subject matter. The amendments are supported, for example, at page 1, lines 22-23, and 30-32; and page 8, lines 20-24 of the specification as filed.

### I. Examiner Interview

Applicant thanks the Examiner for participating in interviews on September 11, 2007, and September 13, 2007 with the undersigned and Dennis Bissonnette. During the interviews, the undersigned and the Examiner discussed the August 28, 2007 Advisory Action and support disclosed in the specification for the amendments made in the August 17, 2007 response. The Examiner noted that the Advisory Action should have stated that the August 17 amendment was not entered because the antecedent basis for the phrase "the individual's endogenous protein" was unclear, and thus indefinite under 35 U.S.C. § 112, second paragraph. Accordingly, the Examiner stated that a Supplemental Advisory Action will therefore be issued. The Examiner also brought to Applicant's attention Handa et al., 2000, "A case of symptomatic heterozygous female Fabry's disease without detectable mutation in the alpha-galactosidase gene," Dermatology 200:262-265 ("Handa"), which the Examiner stated could be used as prior art in an obviousness rejection of the claims.

**II. The Claims Are Definite**

In the interviews with the Examiner, the Examiner stated that the recitation of the phrase "the individual's endogenous protein" in the claims is indefinite for not having the proper antecedent basis. Applicant has amended the claims to recite a method of improving gene therapy by increasing the level of expression of a recombinant protein corresponding to an individual's endogenous protein, which renders the claims definite. As stated on page 8, lines 20-24 of the specification:

> . . . "[G]ene therapy" refers to a method of changing the expression of an endogenous gene by exogenous administration of a gene. . . by introducing a functional gene corresponding to the defective or missing gene into somatic or stem cells of an individual in need.

The invention is directed to a method of treating protein deficiencies by enhancing a gene therapy with an active site-specific chaperone (ASSC) (*see* page 1, lines 13-14 of the specification). The gene introduced exogenously via a gene therapy vector enables the cells of a treated individual to express a functional protein encoded by the vector. Prior to administration of the gene therapy vector, the individual's endogenous version of the protein was deficient due to, for example, "disease or as a side effect of a treatment for a disease (e.g. chemotherapy) or as a result of nutritional insufficiency." Gene therapy is a treatment option when the protein defiency results in a pathological condition (page 1, lines 30-32; and page 9, lines 24-29). The method of the claimed invention therefore improves gene therapy by increasing the level of functional protein encoded by a gene therapy vector to a level that may, for example, achieve therapeutic benefits, wherein the cell, without the benefit of the introduced vector, did not express a sufficient level of its endogenous protein to maintain normal wild-type activity levels. Applicant asserts that the presently amended claims are not indefinite.

**III. Handa**

With regard to the Examiner's statement that Handa could be used in an obviousness rejection of the claims, Applicant respectfully disagrees. Applicant submits that Handa describes a human female subject who exhibited symptoms characteristic of heterozygous female Fabry's disease, including low levels of alpha-galactosidase A in blood plasma. Handa discloses that although the woman exhibited symptoms of the disease, her gene encoding alpha-galactosidase A did not have any detectable mutations in the full coding region of the gene.

Applicant asserts that the presently amended claims would not be obvious in view of Handa. There would be no motivation or expectation of successfully of utilizing chaperone therapy under circumstances described by Handa. As stated by the Examiner in the Final Office Action issued October 4, 2006, "one of skill in the art understands that chaperone therapy is ***only applicable*** to situations in which a mutant protein can be refolded and would act accordingly . . ." (emphasis added, page 11, lines 8-10 of the October 4, 2006, Final Office Action). Conformational disorders result from "mutations that alter protein folding and retardation of the mutant protein in the ER" (page 14, lines 24-26 of the specification). Conformational mutant phenotypes do not result because the proteins are expressed at an insufficient level, but because once expressed, the proteins adopt an inactive conformation, triggering their degradation and preventing the enzymes from interacting with their substrates.

A skilled artisan would not use chaperone therapy under the circumstances disclosed by Handa, wherein the gene encoding the disclosed alpha-galactosidase A contained *no detectable mutation*, such as "partial gene rearrangements, splice junction defects, and point mutations which cause Fabry's disease (*see* page 264, third paragraph, first full paragraph of Handa). Since

the alpha-galactosidase A gene of Handa does not contain any detectable mutation, the protein would not adopt the misfolding phenotype characteristic of Fabry's disease. A skilled artisan, without benefit of the present application, would not elect chaperone therapy as a therapy with a reasonable expectation of successfully treating Handa's subject.

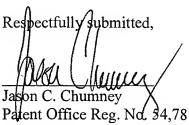
The amended claims are directed to methods of improving gene therapy in individuals whose protein deficiency is such that pharmacological chaperone-based therapy on its own would be expected to have no meaningful effect, as in the condition described by Handa. Instead, the expression-enhancing effects of pharmacological chaperones are claimed in the context of the ability to enhance expression of a therapeutic protein encoded by a therapeutic recombinant gene. Therefore Handa could not form the basis of a valid obviousness rejection.

**IV. Conclusion**

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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